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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/626,677	07/27/2000	Ole Isacson	04843/080001	2582

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/26/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/626,677	ISACSON ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 12-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 12-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 July 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The response filed December 9, 2002 (Paper No. 12) has been entered. Claims 1 and 4 have been amended. Claims 2, 3, and 6-11 have been cancelled. Claims 12-22 have been newly added.

Accordingly, Claims 1, 4, 5, and 12-22 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 9, 2002 (Paper No. 12) has been entered.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The Post Office addresses are incomplete. The ZIP codes are not provided.

A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example pages 19 and 22 of the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, and 5 stand rejected and Claims 12-22 are rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-5 of the Office Action of Paper No. 4 (mailed 10/4/01), on pages 2-6 of the Office Action of Paper No. 9 (mailed 5/31/02), and for further reasons as discussed herein, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a human patient suffering from Parkinson's disease by engrafting into said patient a population of recombinant cells comprising the Nurr-1 gene. Although the preamble implies that the method will result in treatment of Parkinson's disease, no particular treatment effect is achieved.

The specification fails to provide an enabling disclosure for the genetic modification of human ES cells. The recent literature addresses the difficulties encountered in attempting to transfect human ES cells. Zwaka et al. (2003) points out that there are significant differences between mouse and human ES cells and that "[h]igh, stable transfection efficiencies in human ES cells have been difficult to achieve, and, in particular, electroporation protocols established for mouse ES cells work poorly in human ES cells" (abstract). Thus, it is clear that the behavior of mouse ES cells is not predictive of human ES cells.

In April 2001, Eiges et al. compared the efficiency of several different transfection protocols for human ES cells. The reference demonstrates use of the transfection protocol of ExGen 500 to transfect human ES cells. However, the instant specification teaches the use of adenovirus transduction for the genetic modification of human ES cells. Example 6 of the specification describes the transfection of human ES cells with an adenovirus carrying the β-galactosidase reporter gene. Although the disclosure states that "[s]taining for expression of the β-galactosidase marker gene was performed," no results are provided with regard to the detection of β-galactosidase-expressing cells. Thus, at the time of filing, methods for successfully transfecting human ES cells were not known. The teachings of Eiges et al. (2001) would not have been available to the skilled artisan as of the filing date of this application which is July 27, 2000.

The Declaration of Ole Isacson, filed December 9, 2002 (Paper No. 13) has been fully considered but is not found to be persuasive for the following reasons. First, the teachings of the publications to which the Declaration refers are limited to the use of mouse ES cells. For the reasons discussed herein above, the behavior of mouse ES cells is not predictive of the behavior of human ES cells, particularly with regard to transfection protocols. Second, the teachings of the publications are limited to the use of ES cells, whereas the claims continue to broadly recite the use of any and all types of stem cells. For reasons of record, the applicability of the claimed method to a wide variety of different types of stem cells is unpredictable. For reasons of record, the post-filing art discussed in the Declaration does not constitute working examples of the **claimed** invention, which would require the use of human ES cells.

At page 5, paragraphs 2-3 of the response, Applicants argue that the amended claims no longer require the *in vivo* expression of a therapeutic protein or exogenous DNA. Applicants further argue that the exogenous DNA encoding Nurr-1 or PTX-3 is expressed *in vitro* to cause a cell fate determination. However, this is not sufficient to overcome the enablement rejection because, as discussed in the previous Office Actions, the transplanted cells must produce replacement neurons at the critical locations. Furthermore, these replacement neurons must have the appropriate phenotype necessary to correct the

deficiency caused Parkinson's disease. The specification teaches that "it is desirable to transplant cells that are genetically modified to survive the insults that caused the original neurons to die" (p. 18, lines 1-3). Moreover, the specification does not teach how to practice the claimed method to produce replacement neurons of the desired phenotype at the critical locations through the *in vivo* differentiation of embryonic stem (ES) cells transplanted into the brain. These replacement neurons must also integrate into the tissues in a functional manner. The specification contemplates that transfecting the ES cells with one transcription factor gene or the right combination of several transcription factor genes will be sufficient to direct the cells to differentiate *in vivo* into the appropriate cell type and functionally integrate into the tissue into which they are implanted. However, the state of the art for *in vivo* differentiation of ES cells is undeveloped. While much work has been done to develop techniques for the directed differentiation of ES cells *in vitro* to produce desired cell types, little is known about the behavior of these cells *in vivo* or how they will interact with the local environment when implanted into adult tissues. Jackowski (1995) details the limitations and unpredictability associated with the transplantation of neural tissue.

At page 6, paragraph 1 of the response, Applicants again argue that Dr. Isacson describes "successful results of transplanting Nurr-1-expressing ES cells using techniques that are substantially identical to those disclosed in the specification in Example 4." However, it is again noted that the **claimed** invention is directed to treatment of Parkinson's disease, which is a disease of humans. For reasons of record, and as reiterated herein above, results obtained using mouse ES cells are not considered predictive of results that can be achieved in humans, using the same protocols. Furthermore, it is noted that the "successful results" to which Applicants refer were obtained using ES cells, but the claims are broadly directed to the use of any type of stem cell. In view of the guidance of the MPEP, these examples do not constitute working examples and would not be considered to correlate with results in humans.

Given the lack of applicable working examples, the limited guidance provided in the specification, the broad scope of the claims with regard to the wide variety of stem cell types that could be used, and the unpredictability for achieving a therapeutic effect upon the transplantation of human ES cells, undue experimentation would have been required for one skilled in the art to practice the claimed method of the invention in a human patient for therapeutic benefit.

Thus, the rejection under 35 U.S.C. 112, first paragraph, is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4, 5, and 12-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4, 5, and 12-22 are indefinite in their recitation of "a method of treating a human patient suffering from Parkinson's disease" because the preamble implies that a treatment effect will be achieved, but in fact no particular treatment effect is achieved. Thus, the preamble is in conflict with the body of the claim.

Claims 1, 4, 5, and 12-22 are indefinite in their recitation of "cells which are lineage-restricted to dopaminergic neurons" and "lineage-restricted cells" because it is unclear if this claim language is intended to include dopaminergic neurons or if it only includes precursor cells that are not dopaminergic neurons. Thus, the metes and bounds are not clearly set forth.

Claims 1, 4, 5, and 12-22 are indefinite in their recitation of "said lineage-restricted cells of step (c)" because the phrase lacks antecedent basis.

Claims 1, 4, 5, and 12-22 are indefinite in their recitation of "transfecting said stem cells with Nurr-1" or "transfecting said stem cells with PTX-3" or similar language, because Nurr-1 and PTX-3 are proteins and one would not "transfect" a cell with a protein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Lindvall et al. (1992).

Claim 19 is directed to a method of treating a human patient suffereing from Parkinson's disease by engrafting into said patient cells which are lineage-restricted to dopaminergic neurons.

Lindvall et al. (1992) disclose the successful transplantation of fetal dopaminergic neurons into patients having Parkinson's disease.

Thus, the claimed invention is disclosed in the prior art.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER